Improving Visual Attention to Social Stimuli in Individuals with Schizophrenia.

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Current Research Program

It is unclear what causes the social cognitive deficits that are observed in schizophrenia, but one promising theory suggests that abnormal visual attention may prevent accurate understanding of social information, cascading into more complex social dysfunction. Specifically, we propose that faulty modulation of the rTPJ, which is possibly responsible for updating internal models with appropriate and salient external information, leads to abnormal visual attention in the form of abnormal scanning and fixations when viewing both social and nonsocial stimuli. The failure to attend to salient visual stimuli may then prevent accurate social cognitive processes that are intrinsically tied to functional outcomes. As these social deficits are tied to daily functioning, it is of interest to parse out this relationship and determine if abnormal neural modulation underlies visual attention abnormalities. Novel neurostimulation techniques provide a viable method for addressing this question as they allow for the experimental manipulation of neural regions that can extend to neural networks, resulting in a range of observable effects in both healthy individuals and clinical populations.

The current research program therefore seeks to experimentally manipulate the neural mechanism that potentially underlies the automatic behavioral process of visual attention. Through the use of novel neurostimulation techniques (i.e., anodal tDCS to rTPJ) and eye tracking technology, we aim to directly assess how rTPJ impacts visual attention to social stimuli.

Considerations

One consideration for this study is to address whether any observed changes are specific to stimulation of the TPJ. In order to address these concerns, we will use an alternate stimulation site as a comparator. The dorsal medial prefrontal cortex (dmPFC) may act as a suitable alternate

stimulation site, as it has a role in controlled integration of information within the social brain network[1]. However, unlike the TPJ, the dmPFC should not directly be involved in reorienting visual attention to salient cues. Comparing stimulation of rTPJ to that of dmPFC should therefore allow examination of the dissociable role of stimulus driven attention via the rTPJ vs. cognitive control over social cognition via dmPFC. To limit practice effects on our social cognitive tasks, we will not require participants to undergo active and sham stimulation conditions to both brain regions. Instead, after pairing participants on key demographic factors (i.e. age, race, and, when possible, years of education), we will randomly assign participants to receive active and sham conditions over either the TPJ or dmPFC and use stimulation site as a between subject's factor.

Aims and Hypothesis.

The current research program investigates the role of the TPJ, specifically the right TPJ, in visual attention and how this may act as one potential mechanism for social cognitive impairments in individuals with schizophrenia. Primarily, we seek to utilize anodal tDCS to stimulate the rTPJ in order to increase the proportion of time spent attending to salient visual social stimuli compared to sham stimulation as measured via eye-tracking.

In order to support the overarching idea that abnormal visual attention stems from dysregulated neural systems, we hypothesize the following:

1. Participants will better regulate their eye movements (i.e. show a higher percentage of fixations in designated areas of interest) after anodal stimulation of the rTPJ relative to sham, and compared to stimulation of the dmPFC.

Should improvements in visual attention occur only after anodal stimulation to the rTPJ, we will have demonstrated that visual attention to socially salient stimuli can be impacted by tDCS based

upon increased electrical activation in this region. We expect to see no significant increase in visual attention after stimulation of our comparator site, the dmPFC.

Methods

Participants. This study will recruit participants diagnosed with schizophrenia or schizoaffective disorder (DSM-5 codes 295.9 and 295.7) between the ages of 18 and 65. Upon entry into the study, participants will be randomly assigned to one of the two stimulation location groups, the TPJ stimulation group and the dmPFC stimulation group.

Patients will be recruited from a laboratory database of past participants, as well as through mental health agencies servicing the Dallas- Fort Worth metroplex. Psychiatric diagnoses will be confirmed through the administration of two gold standard diagnostic assessments, *Mini International Neuropsychiatric Interview* (MINI)[2] and *Structured Clinical Interview for DSM Disorders - Psychosis Module* (SCID-P)[3]. Prescribed medications will be assessed via patient self-report as well as medical and pharmacy records as available, and participants will be asked to remain on stable dose of medication throughout their participation in the study.

Participants will be deemed ineligible for this study if they meet any of the following additional criteria: i) the presence or history of a pervasive developmental disorder or mental retardation as defined by a premorbid IQ < 70, ii) presence or history of medical or neurological disorders in which neural stimulation would be contraindicated (e.g. presence of epilepsy or history of seizures, iii) presence of sensory limitations, including visual or hearing impairments that interfere with assessment, iv) history of electroconvulsive therapy, v) not proficient in English, vi) presence of substance abuse in the past one month or dependence not in remission in the past six months. Participants will be matched in pairs based upon key demographic factors,

specifically age (within 5 years of age) and race, as well as years of education when able. Paired participants are not expected to complete the study at the same time, but instead will act as comparators for the two stimulation locations. Each member of the participant pair will be assigned to one of the two identified tDCS stimulation locations (i.e. either the TPJ or the dmPFC) prior to enrollment and assessment.

Procedure/ Design. Participants will be asked to complete two visits with 7 to 10 days between the two visits to allow for any tDCS effects from the first visit to dissipate. At the initial visit, and prior to any study specific tasks, written informed consent will be obtained from the participant. Participants will complete two diagnostic interviews to confirm psychiatric diagnosis. The MINI and SCID-P will be administered as needed for all subjects whose psychiatric diagnosis have not previously been confirmed by a trained member of the research team in a previous lab study.

Stimulation procedure. Following diagnostic and symptom assessment interviews, subjects will begin the neurostimulation procedure using neuroConn's programable Direct Current stimulator.

During the neurostimulation procedure, electrodes will be affixed to the subject's head in order to target the assigned stimulation location. Placement will be determined for each individual using international 10-20 EEG placement system with Modified Combinatorial Nomenclature. For those assigned to the target TPJ region, the anode will be placed between P6 and CP6, which will target the posterior portion of the TPJ. Although the electrodes are too large to target specific sub regions of the rTPJ, this placement should sufficiently stimulate the posterior portion of the rTPJ that may be associated with social cognitive function, as well as attentional reorientation. The cathode for this montage will be placed extra-cortically on the left

shoulder. Placing the cathode contralaterally will draw the current across the midline, ensuring full stimulation of the targeted region.

For those assigned to the dmPFC target location, the anode will be placed at AFz, with the cathode placed on the opposite side of the skull, on the participant's neck, approximately 1 cm below Iz. This location is desired to ensure the current flows through the targeted dmPFC region.

For all participants, active and sham stimulation will be counterbalanced, so that each participant will have an equal likelihood of receiving either active or sham stimulation at their first visit, and the alternate at their second. NeuroConn machine's preprogrammed "study mode" will be used to administer either active or sham stimulation in a double-blinded fashion. This is accomplished through the use of preprogrammed, 5-digit stimulation codes that the administrator will manually enter into the device prior to each stimulation procedure that indicates whether that condition is to be active or sham. These 5-digit codes will be paired, one active code and one sham code, prior to study start so that a single participant cannot inadvertently be assigned to two active or two sham conditions. Codes entered into the machine at each visit will be recorded for unblinding after study completion. A master list that identifies which condition relates to each code will be accessible only by the lab director during the duration of the study in the event the blind needs to be broken in real time.

The total stimulation procedure time will be 20 minutes and 30 seconds for both active and sham stimulation. The active stimulation will consist of active current at 2mA, ramping up over 15 seconds, sustaining for 20 minutes, and then ramping down for an additional 15 seconds. In the pre-programmed sham condition, the procedure will consist of a brief active current that will follow the same ramping procedure as the active condition, 15 seconds ramping up and 15

seconds ramping down. Unlike the active condition, the participant will only receive 30 seconds of direct current before the ramp down occurs. The machine will continue to perform impedance control checks during the remainder of the 20-minute assessment so that the participant and the administrator are unaware of which condition the machine is administering.

Following the neurostimulation procedure, the participant will be asked to wait quietly and read through a selection of magazines for 30 minutes to allow for tDCS effects to work through the neural network. Participants will then complete the remaining behavioral measures with concurrent eye movements recorded via Gazepoint desktop eye tracker. Gazepoint is an eye tracking system that can easily be attached to the bottom of a computer monitor, and angled toward the participant's eyes in order to capture visual attention to stimuli shown on the computer screen.

Post-stimulation assessments. Following the stimulation procedures, subjects will complete a series of three social cognitive tasks and a visual fixation task. Poststimulation tasks will be counterbalanced to reduce the impact of practice or order effects on our results. The same tasks will be administered following both active and sham stimulation.

Social cognitive tasks. Descriptions for each of the social cognitive tasks are listed below. Eye tracking will be utilized to measure the primary variable, the proportion of time attending to researcher identified socially and contextually important cues in the social cognition tasks. The method for identification of socially and contextually important cues discussed in the statistical plan below and examples of these important areas of interest (AOIs) are discussed in the task descriptions.

- *Emotion Recognition 40* (ER-40)[4]. Participants will be shown 40 color photographs of faces expressing 4 basic emotions (i.e. happiness, sadness, anger, or fear) and neutral

expressions, one at a time, and asked to identify the emotion expressed on each face. Socially important AOIs for this task will be core features of the faces shown, namely the eyes, nose, and mouth of the actors exhibiting the emotions.

- *Bell Lysaker Emotion Recognition Task* (BLERT)[5]. Participants will view 21 ten second video clips of a male actor expressing one of seven emotional states (i.e. happiness, sadness, fear, disgust, surprise, anger, and no emotion). In this task, socially important AOIs will be similar to static faces in the ER40, namely the core features of the actor's face, in addition to the actor's body movement during the video.
- *The Awareness of Social Inferences Test* (TASIT)[6]. Participants will view 16 video vignettes of complex social situations in which actors either use lies or sarcastic responses to relay information to the other actors in the scene. For this task, both socially and contextually important AOIs will be identified. Socially important AOIs will be similar to the previous two tasks, namely core features of the actors' faces and bodies. Contextually important AOIs will be specific to each scene, but include specific clues embedded in the scene that are needed to understand the intent of the main actor in each scenario. Examples of these contextually important cues include childlike scribbles in a book, an empty wallet, or an incomplete crossword puzzle.

Non-Social Eye Movement task. Following research that identifies both scanpath abnormalities on freeviewing tasks and unstable fixations on directed tasks as potential markers of schizophrenia,[7] this task will be included as a supplementary assessment to characterize the extent to which stimulation of our targeted areas affects visual abnormalities observed in the disorder. Since the rTPJ is believed to be responsible for reorienting attention only when stimuli is behaviorally or contextually relevant, it is hypothesized that participants should have better

stability of visual attention post TPJ stimulation relative to sham and compared to dmPFC stimulation as distractors will not be behaviorally relevant.

- *Fixation task.* (Adapted from Benson et al., 2015)[7] Participants will be instructed to focus on a single fixation cross presented in the middle of the screen for a 5 second interval. The fixation cross will either be presented alone in the center of the screen, or with flanking distractor fixation crosses presented on either the left or right side of the screen, totaling three conditions. Each condition will be presented in random order two times, for a total of six fixation assessments. Eye tracking software will be utilized to measure eye drift from the center fixation cross during each of the conditions to calculate fixation stability.

Statistical plan. To test this study's primary hypothesis, which predicts that anodal stimulation of the TPJ will increase the proportion of time spent attending to salient visual stimuli, we will first identify and mark salient areas of interest (AOI) on the social cognitive tasks as discussed in the task descriptions above. For all tasks, AOI's will be determined based upon consensus review of each stimulus/scene by expert researchers (HK and AEP). Should the researchers fail to agree on specific AOIs, a third opinion will be solicited from a researcher in the field with experience administering the task. A two-thirds majority opinion will determine any contested AOI.

Once primary eye tracking values are obtained, we will run three separate 2x2 mixed ANOVAs on the proportion of time spent attending to researcher defined regions of interest on static faces (ER-40), dynamic videos (BLERT), and social situations (TASIT), with location (TPJ vs dmPFC) as a between subjects' factor and stimulation condition (active versus sham stimulation) as a within subject factor. No direct comparisons between tasks will be performed as

we do not have any hypotheses regarding if the effect will be larger for one social cognitive task versus any other. We hope to observe simple main effects for region (TPJ > dmPFC) and stimulation type (active > sham), but expect that if these main effects are observed, they will be accounted for by interaction effects between location and stimulation condition. Specifically, should active stimulation on the TPJ increase proportion of time attending to AOIs compared to all other conditions, this interaction effect would support our hypothesis that TPJ activation has a unique effect on visual attention during all tasks. To adjust for multiple comparisons, a Bonferroni correction will be applied, with significant alpha = 0.017 for each of the tests run.

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